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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 12/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,763	AKHAVAN-TAFTI ET AL.	
	Examiner	Art Unit	
	Stephanie K. Mummert	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-50 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-30 and 32-50 is/are rejected.

7)☒ Claim(s) 31 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 8/19/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on August 19, 2005 is being considered by the examiner. Examiner notes that there are typographical errors in the patent documents listed on page 2 of the statement. Reference Z on page 2 of the IDS is listed as US Patent 6,063,892, but that patent number points to a patent in a different art with a different inventor, while US Patent 6,036,892 is the patent number matching the rest of the entry. A similar situation occurred with Reference MM on page 2, where the number should apparently be corrected to US Patent 5,075,730.

2. The information disclosure statement filed August 19, 2005 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language, namely references T-V. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1, 6-12, 19-22, 30, 32-35, 42-46, 48 and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Summerton et al. (US Patent 6,060,246; May 2000). Summerton teaches methods for rapidly detecting and isolating target nucleic acid sequences from a polynucleotide containing solution (Abstract, lines 1-3).

With regard to claim 1, Summerton teaches a method of isolating a nucleic acid from a sample, comprising the steps:

a) providing a solid phase comprising: a solid support portion comprising a matrix of silica, glass, insoluble synthetic polymers and insoluble polysaccharides (col. 5, lines 13-60, where glass beads, or beads with polyethylene glycol linkages to reduce binding of undesirable components, and the use of magnetic particles are discussed); a nucleic acid binding portion for attaching and binding nucleic acids, and a cleavable linker portion (col. 7, lines 15-17 and col. 8, line 64 to col. Col. 9, line 42, where the cleavable linker can include disulfide, esters, orthonitrobenzyl esters, peptides and oligosaccharides);

b) combining the solid phase with the sample containing the nucleic acid to bind the nucleic acid to the solid phase (col. 9, lines 43-48, where the sample is contacted with a "rapid-pairing reagent");

c) separating the sample from the solid phase (col. 9, lines 48-49, where non-specifically bound nucleotides are released; see also col. 18, lines 64 to col. 19, line 17);

d) cleaving the cleavable linker (col. 12, lines 19-28); and

e) releasing the nucleic acid from the solid phase (col. 12, lines 19-28 or lines 29-36).

With regard to claim 6 and 9-10, Summerton teaches an embodiment of claim 1, wherein the solid support portion is selected from particles, microparticles and beads (col. 5, lines 46-60), glass or silica (col. 5, lines 34-45).

With regard to claim 7, Summerton teaches an embodiment of claim 1, wherein the solid support portion comprises an insoluble synthetic polymer (col. 2, lines 50-56, where the binding portion can comprise a peptide nucleic acid or a polynucleotide analog; see also col. 14, lines 10-15, where morpholino oligomers are used for either a target-specific or capture portion that are non-extendable by polymerases).

With regard to claim 8, Summerton teaches an embodiment of claim 7, wherein the polymer is selected from polystyrene and polyacrylic polymers (col. 18, lines 54-56, where the microparticles comprise polystyrene).

With regard to claim 11, Summerton teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase further comprises one or more connecting portions (col. 9, lines 38-42, where a spacer group or additional linkage groups can connect the capture component to the reagent surface).

With regard to claim 12, Summerton teaches an embodiment of claim 1, wherein the solid phase further comprises a magnetically responsive portion (col. 5, lines 13-60, where glass beads, or beads with polyethylene glycol linkages to reduce binding of undesirable components, and the use of magnetic particles are discussed; see also col. 18, lines 34-55).

With regard to claim 19, Summerton teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase is cleaved reductively (col. 9, lines 28-31, where the disulfide is cleaved with a sulfhydryl).

With regard to claim 20, Summerton teaches an embodiment of claim 19, wherein the cleavable linker comprises a disulfide group (col. 2, lines 41-43; see also col. 9, lines 28-31).

With regard to claim 21, Summerton teaches an embodiment of claim 19, wherein the reductive cleavage is performed with a reducing agent selected from thiols, amines and phosphines. (col. 9, lines 28-31, where the disulfide is cleaved with a sulfhydryl).

With regard to claim 22, Summerton teaches an embodiment of claim 21, wherein the reducing agent is selected from 2-mercaptoethanol or dithiothreitol (col. 9, lines 28-31).

With regard to claim 30, Summerton teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase is cleaved enzymatically (col. 9, lines 28-37, where the enzymes disclosed include esterases, peptidases, proteases, oligosaccharidases, glycosidases).

With regard to claim 32, Summerton teaches an embodiment of claim 30, wherein the cleavable linker portion of the solid phase comprises an ester which is cleaved by hydrolase enzyme (col. 2, lines 41-45; see also col. 9, lines 28-37).

With regard to claim 33, Summerton teaches an embodiment of claim 30, wherein the cleavable linker portion of the solid phase comprises an amide which is cleaved by a protease enyme (col. 9, lines 28-37, where peptides are cleaved by peptidases or proteases).

With regard to claim 34, Summerton teaches an embodiment of claim 30, wherein the cleavable linker portion of the solid phase comprises a peptide which is cleaved by a peptidase

(col. 2, lines 41-45; see also col. 9, lines 28-37, where peptides are cleaved by peptidases or proteases).

With regard to claim 35, Summerton teaches an embodiment of claim 30, wherein the cleavable linker portion of the solid phase comprises a glycoside which is cleaved by a glycosidase (col. 2, lines 41-45; see also col. 9, lines 28-37, where oligosaccharides are cleaved by glycosidases).

With regard to claim 42, Summerton teaches an embodiment of claim 1, wherein the cleaving reaction and elution steps are performed as sequential steps using separate and distinct solutions to accomplish each step (col. 5, lines 1-7, where non-target polynucleotides are released through cleavage of linkers, followed by elution of target molecules in a subsequent step).

With regard to claim 43, Summerton teaches an embodiment of claim 1, wherein the cleaving and elution steps can be performed together in the same step (col. 6, lines 58-64, where a strongly basic amine is used in the capture component and bound molecules are released by selective cleavage of the linkage instead of through elution with adjustments to pH of solutions).

With regard to claim 44, Summerton teaches an embodiment of claim 1, further comprising, after step b) washing the solid phase having captured nucleic acid bound thereto with a wash solution to remove other components of the sample from the solid phase (col. 18, line 64 to col. 19, line 17, where multiple buffer washes were used prior to release/elution of bound target polynucleotides).

With regard to claim 45, Summerton teaches an embodiment of claim 1, wherein the step of separating the sample from the solid phase is accomplished by magnetic separation (col. 18,

lines 64 to col. 19, line 17, where magnetic separation was used in the isolation of poly-A tailed alpha globin RNA).

With regard to claim 46, Summerton teaches an embodiment of claim 1, wherein the step of separating the sample from the solid phase is accomplished by a process selected from centrifugation and vacuum aspiration (col. 19, lines 8-11, where supernatant was aspirated).

With regard to claim 48, Summerton teaches an embodiment of claim 1 further comprising: a) releasing the nucleic acid from the solid phase in step e) into a solution (col. 14, lines 16-24); and

b) using the solution containing the released nucleic acids directly in a downstream process (col. 14, lines 16-24).

With regard to claim 50, Summerton teaches an embodiment of claim 49, wherein the solution containing the released nucleic acid is used directly in a nucleic acid amplification reaction whereby the amount of the nucleic acid or segment thereof is amplified using a polymerase or ligase-mediated reaction (col. 14, lines 16-24).

5. Claims 1, 6-7, 9-12, 19-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Lough et al. (US Patent 5,900,481; May 1999). Lough teaches compositions of beads conjugated to nucleic acids (Abstract)

With regard to claim 1, Lough teaches a method of isolating a nucleic acid from a sample, comprising the steps:

a) providing a solid phase comprising: a solid support portion comprising a matrix of silica, glass or insoluble synthetic polymers (col. 3, lines 15-24, where the bead can be silica, glass, resin,

sepharose, or plastic, for example; see also col. 3, lines 25-37); a nucleic acid binding portion for attaching and binding nucleic acids, and a cleavable linker portion (Figure 1, see also col. 2, lines 40-50; see also col. 3, lines 37-52, where the different types of linkers are described);

b) combining the solid phase with the sample containing the nucleic acid to bind the nucleic acid to the solid phase (example 2, col. 6, lines 45-53);

c) separating the sample from the solid phase (example 4, lines 24-46, where the nucleic acid bound beads are separated and bound to an additional solid phase);

d) cleaving the cleavable linker (col. 3, lines 37-52); and

e) releasing the nucleic acid from the solid phase (col. 4, lines 47-52, where the nucleic acid may be removed; see also col. 5, lines 18-30, where different embodiments of selective cleavage of different linkers are envisioned).

With regard to claim 6 and 9-10, Lough teaches an embodiment of claim 1, wherein the solid support portion is selected from particles, microparticles and beads and glass or silica (col. 3, lines 15-24, where the bead can be silica, glass, resin, sepharose, or plastic, for example; see also col. 25-37).

With regard to claim 7, Lough teaches an embodiment of claim 1, wherein the solid support portion comprises an insoluble synthetic polymer (col. 3, lines 15-24, where the bead can be silica, glass, resin, sepharose, or plastic, for example; see also col. 3, lines 25-37).

With regard to claim 11, Lough teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase further comprises one or more connecting portions (Figure 1, where there are two different linkages, one connecting the bead to the nucleic acid and another connecting the bead to a solid support).

With regard to claim 12, Lough teaches an embodiment of claim 1, wherein the solid phase further comprises a magnetically responsive portion (col. 4, lines 53-58).

With regard to claim 19, Lough teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase is cleaved reductively (col. 5, lines 18-30, where a disulfide linker is contemplated for both types of linkers and where the disulfide linkage would be cleaved using DTT).

With regard to claim 20, Lough teaches an embodiment of claim 19, wherein the cleavable linker comprises a disulfide group (col. 5, lines 18-30, where a disulfide linker is contemplated for both types of linkers and where the disulfide linkage would be cleaved using DTT).

With regard to claim 21, Lough teaches an embodiment of claim 19, wherein the reductive cleavage is performed with a reducing agent selected from thiols, amines and phosphines. (col. 5, lines 18-30, where a disulfide linker is contemplated for both types of linkers and where the disulfide linkage would be cleaved using DTT).

With regard to claim 22, Lough teaches an embodiment of claim 21, wherein the reducing agent is selected from 2-mercaptoethanol or dithiothreitol (col. 5, lines 18-30, where a disulfide linker is contemplated for both types of linkers and where the disulfide linkage would be cleaved using DTT, which is an abbreviation for dithiothreitol).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 2 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Summerton et al. in view of Seligson et al. (US Patent 4,935,342; January 1990) and further in view of Platz et al. (US Patent 5,418,130; May 1995) or Hatekeyama et al. (JP2002060671; February 2002). Summerton teaches methods for rapidly detecting and isolating target nucleic acid sequences from a polynucleotide containing solution (Abstract, lines 1-3). Summerton teaches the limitations of claims 1, 6-12, 19-22, 30, 32-35, 42-46, 48 and 50 as recited in the 102 rejection stated above.

Summerton teaches the isolation of nucleic acid molecules using cleavable linkage attachments between the nucleic acid binding portion and the surface of the solid support. Summerton does not teach of the use of quaternary ammonium, phosphonium or ternary sulfonium groups for binding of nucleic acids, however amine groups are discussed. Seligson teaches a method of separation, isolation and purification of DNA or RNA from biological samples using quaternary ammonium groups for binding (col. 3, lines 56-66, where beds of anion exchange material are used; see also Table found under col. 5/6, where specific types of anion exchange materials are described in detail, with specific notice of QMA and QAE columns, which contain quaternary ammonium groups).

Regarding claim 2, Seligson also teaches that the nucleic acid binding portion comprises a quaternary ammonium group NR3+X, wherein R is selected from alkyl and wherein X is an anion (col. 5, lines 1-65, specifically lines 33-37 and 56-65, where the quaternary group is usually dimethylammonium or trimethylammonium and where the anion is chloride).

With regard to claim 49, Seligson in view of Summerton teaches a method comprising: a) releasing the nucleic acid from the solid phase in step e) into a solution (col. 14, lines 16-24); and b) using the solution containing the released nucleic acid directly in a downstream process (col. 14, lines 16-24).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include the cleavable linkers taught by Summerton in the isolation technique taught by Seligson. As taught by Summerton, "the present invention, by combining rapid capture and concentration of polynucleotides with selective targeting of analyte molecules greatly enhances this process" in contrast to the "generally very slow and inefficient, especially for low-copy sequences" process of conventional hybridization to sequence-specific probes (col. 14, lines 4-15). One of ordinary skill in the art at the time the invention was made would recognize the benefit of enhanced isolation of nucleic acid molecules and would make particular note of the embodiment which incorporates sequence specific capture of nucleic acid molecules in addition to cleavable linkers, which allow for "selective retention on the reagent surface of a target sequence containing polynucleotide" (col. 8, lines 64-67). The selective retention of target sequences could be amplified on the bead, because "amplification may conveniently be carried out without release of analyte molecule from the rapid pairing reagent, as long as the amplicon region is outside of the target sequence bound to the target specific probe" (col. 14, lines 20-24).

One of ordinary skill would recognize the benefit of the cleavable linkers and nucleic acid capture techniques taught and the potential for enrichment of specific target sequences, who would therefore be motivated to incorporate the cleavable linkers and target specific capture molecules into the nucleic acid capture technique taught by Seligson with a reasonable expectation of success.

8. Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Summerton et al. in view of Seligson et al. (US Patent 4,935,342; January 1990) and further in view of Platz et al. (US Patent 5,418,130; May 1995) or Hatekeyama et al. (JP2002060671; February 2002). Summerton teaches methods for rapidly detecting and isolating target nucleic acid sequences from a polynucleotide containing solution (Abstract, lines 1-3). Summerton teaches the limitations of claims 1, 6-12, 19-22, 30, 32-35, 42-46, 48 and 50 as recited in the 102 rejection stated above. Summerton teaches the isolation of nucleic acid molecules using cleavable linkage attachments between the nucleic acid binding portion and the surface of the solid support. Summerton does not teach of the use of quaternary ammonium, phosphonium or ternary sulfonium groups for binding of nucleic acids, however amine groups are discussed.

Seligson teaches a method of separation, isolation and purification of DNA or RNA from biological samples using quaternary ammonium groups for binding (col. 3, lines 56-66, where beds of anion exchange material are used; see also Table found under col. 5/6, where specific types of anion exchange materials are described in detail, with specific notice of QMA and QAE columns, which contain quaternary ammonium groups).

In addition to the quaternary ammonium taught by Seligson, Platz teaches the inclusion of ammonium or phosphonium substituted halo-psoralen compound for the inactivation of viral or bacterial contamination in the blood (Abstract). Platz teaches an embodiment of claim 1 wherein the nucleic acid binding portion of the solid phase is selected from a quaternary phosphonium group PR3+X- wherein R is selected from C1-C20 alkyl, aralkyl, and aryl groups, and wherein X is an anion (col. 6, lines 22-40 and col. 52, lines 51-64, where (3-Bromo)propyltriethylphosphonium bromide was synthesized).

With regard to claim 3, Platz teaches an embodiment of claim 2, wherein the nucleic acid binding portion is a quaternary ammonium group and the R groups each contain from 4-20 carbon atoms (col. 51, lines 1-67, where 3-[8-(2,3,9-Tribromopsoralen)oxy]propyltriethyl ammonium bromide; 2-[8-(2,3,9-Tribromopsoralen)oxy]proppyldimethyl-2-dimethylamminoethyl ammonium bromide; and 3-[8-(2,3,9-Tribromopsoralen)oxy]propyl-(2-hydroxyl)ethyldimethylammonium bromide were synthesized).

With regard to claim 4, Platz teaches an embodiment of claim 2, wherein the nucleic acid binding portion is a quaternary phosphonium group and the R groups each contain from 1-20 carbon atoms (col. 52, lines 51-64, where (3-Bromo)propyltriethylphosphonium bromide was synthesized).

With regard to claim 5, Platz teaches an embodiment of claim 4, wherein each R group of the solid phase is a butyl group (claim 38, where R', R'', and R''' are methyl, ethyl, n-propyl or n-butyl).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute a ternary phosphonium group or a ternary sulfonium group for

the quaternary ammonium group taught by Seligson. As taught by Platz, the inclusion of an ammonium or phosphonium group within the sensitizer of their claimed invention "can impart water solubility to the sensitizer molecule" and also that "the substitution of halogen atoms, particularly bromine atoms, or psoralen molecules increases the binding constant of the sensitizer to DNA" (col. 4, lines 31-35 and col. 6, lines 28-32). Further, as taught by Hatakeyama, the ammonium, phosphonium or sulfonium groups retain their positive charge. The improvement in binding to nucleic acids through the inclusion of one of these functional groups allows for stable binding of nucleic acids. The benefit of improved affinity for nucleic acids to a particular solid phase would be obvious to one of ordinary skill in the art who would therefore be motivated to include a phosphonium or sulfonium group where quaternary ammonium groups have been used in the past with a reasonable expectation of success.

9. Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Summerton et al. in view of Seligson et al. (US Patent 4,935,342; January 1990) and further in view of Platz et al. (US Patent 5,418,130; May 1995) or Hatekeyama et al. (JP2002060671; February 2002). Summerton teaches the limitations of claims 1, 6-12, 19-22, 30, 32-35, 42-46, 48 and 50 as recited in the 102 rejection stated above. Summerton teaches the isolation of nucleic acid molecules using cleavable linkage attachments between the nucleic acid binding portion and the surface of the solid support. Summerton does not teach of the use of quaternary ammonium, phosphonium or ternary sulfonium groups for binding of nucleic acids, however amine groups are discussed.

Seligson teaches a method of separation, isolation and purification of DNA or RNA from biological samples using quaternary ammonium groups for binding (col. 3, lines 56-66, where beds of anion exchange material are used; see also Table found under col. 5/6, where specific types of anion exchange materials are described in detail, with specific notice of QMA and QAE columns, which contain quaternary ammonium groups).

Seligson does not mention the use of a sulfonium group, but Hatakeyama et al. teaches an equivalence between ammonium, phosphonium and sulfonium groups attached to a resin for binding nucleic acids, proteins or peptides.

With regard to claim 47, Hatakeyama teaches an embodiment of claim 2, wherein the nucleic acid binding portion of the solid phase is a ternary sulfonium group of the formula SR2+X- where R is selected from C1-C20 alkyl, aralkyl and aryl groups, and wherein X is an anion (see entire abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute a ternary phosphonium group or a ternary sulfonium group for the quaternary ammonium group taught by Seligson. As taught by Platz, the inclusion of an ammonium or phosphonium group within the sensitizer of their claimed invention "can impart water solubility to the sensitizer molecule" and also that "the substitution of halogen atoms, particularly bromine atoms, or psoralen molecules increases the binding constant of the sensitizer to DNA" (col. 4, lines 31-35 and col. 6, lines 28-32). Further, as taught by Hatakeyama, the ammonium, phosphonium or sulfonium groups retain their positive charge. The improvement in binding to nucleic acids through the inclusion of one of these functional groups allows for stable binding of nucleic acids. The benefit of improved affinity for nucleic acids to a particular solid

phase would be obvious to one of ordinary skill in the art who would therefore be motivated to include a phosphonium or sulfonium group where quaternary ammonium groups have been used in the past with a reasonable expectation of success.

10. Claim 13-15 and 23-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Summerton in view of Schaap et al. (US Patent 5,707,559; January 1998). Summerton teaches methods for rapidly detecting and isolating target nucleic acid sequences from a polynucleotide containing solution (Abstract, lines 1-3).

Summerton does not explicitly teach the inclusion of dioxetane linkages as a part of the invention disclosed as recited in the 102 rejection stated above, but Summerton does teach the inclusion of cleavable linkages of a variety of forms in the isolation of target nucleic acids. Schaap teaches novel light-producing compounds termed 1,2-dioxetanes which can be triggered to produce light at room temperature (Abstract).

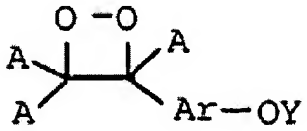
With regard to claim 13, Schaap teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase is cleaved hydrolytically (col. 26, lines 54-65, where the base is potassium hydroxide; col. 27, lines 44-46, where the proof of enzyme-catalyzed hydrolysis begins).

With regard to claim 14, Schaap teaches an embodiment of claim 13, wherein the hydrolytic cleavage is performed with a solution that contains a base selected from hydroxide and alkoxide salts (col. 26, lines 54-65, where the base is potassium hydroxide).

With regard to claim 15, Schaap teaches an embodiment of claim 14, wherein the base is selected from hydroxide salts and alkoxide salts (col. 26, lines 54-65, where the base is potassium hydroxide).

With regard to claim 23, Schaap teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase comprises a triggerable dioxetane ring which is cleaved by a triggering agent (Abstract, see also col. 26, lines 40-65).

With regard to claim 24, Schaap teaches an embodiment of claim 23, wherein the triggerable dioxetane has the formula



wherein the group A represent stabilizing substituents selected from alkyl, cycloalkyl, aryl, aryloxy, and alkoxy (col. 6, lines 43-65, where A, or R1, R3 and R4, is selected from alkyl, alkoxy, aryloxy, and spirofused aryl groups), Ar represents an aryl ring group which can contain additional substituents selected from halogens, alkoxy and amine groups (col. 6, lines 43-65, where R2 is an aryl which can include oxy groups), Y is a group or atom which is removable by a triggering agent selected from the chemical agents and enzymes to cause fragmentation of the dioxetane ring (col. 6, line 43 to col. 7, line 25, wherein OY is an oxy group substituted on an aryl ring which forms an unstable oxide intermediate 1,2-dioxetane compound when triggered to remove Y by an activating agent).

With regard to claim 25, Schaap teaches an embodiment of claim 24, wherein the OY group is selected from OH, $OSiR^3_3$, wherein R^3 is selected from alkyl and aryl groups, carboxyl

groups, phosphate salts sulfate salts and glycoside groups (col. 8, lines 3-12, where OY can be hydroxyl, aryl siloxy and oxygen pyranoside, for example).

With regard to claim 26, Schaap teaches an embodiment of claim 24, wherein Ar in the triggerable dioxetane is a substituted or unsubstituted phenyl or napthyl group (col. 8, lines 3-12, where Ar or R2 is an aryl group that can be a phenyl, biphenyl, fused phenyl and other aryl groups that can contain between 6 and 30 carbon atoms and can include other substituents).

With regard to claim 27, Schaap teaches an embodiment of claim 23, wherein the triggering agent is selected from bases, fluoride ion, a esterase, a phosphatase, a sulfatase, and a glycosidase (col. 26, lines 40- col. 27, lines 28-66, where the triggering agent is selected from bases, fluoride ion and see col. 40; see also col. 8, lines 28-39, where additional triggering agents acids, bases, salts and enymes).

With regard to claim 28, Schaap teaches an embodiment of claim 1, wherein the cleavable linker portion of the solid phase comprises an electron rich alkene, which is cleaved by conversion to a thermally unstable dioxetane (col. 8, lines 49-67).

With regard to claim 29, Schaap teaches an embodiment of claim 28, wherein the alkene is converted to the unstable dioxetane by reaction with a singlet oxygen (col. 8, lines 49-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the dioxetane compound taught by Schaap into the DNA binding compound which incorporated cleavable linkers in the isolation of target nucleic acid molecules. As taught by Schaap, the dioxetane compound is a "novel stable 1,2-dioxetanes which can be decomposed with an activating agent to form light and two carbonyl compounds" and furthermore, a compound that is stable at room temperature for an extended period of time,

that is activatable by chemical and biochemical means, and which can generate light (col. 5, lines 22-34). At the time the invention of Schaap was made, dioxetane compounds were known to be capable of chemiluminescence, but the compounds were unstable or needed to be reacted under conditions unfavorable to evaluation of biological macromolecules (col. 1-3). With the improvements made with the synthesis of the compound taught by Schaap, the dioxetane compound provides a stable compound, capable of being cleaved by enzymatic or chemical means and yields stable fluorescence. The target nucleic acid isolation technique taught by Summerton has an embodiment directed to the isolation of specific target nucleic acids. Summerton teaches the use of multiple types of linkers to connect the different capture portions of the solid phase and it would be obvious to include another variation, particularly one as versatile as the dioxetane compound taught by Schaap. One of ordinary skill in the art would recognize the benefit of luminescence upon cleavage of a cleavable linkage used in the isolation of nucleic acids, and the additional benefits of a thermally stable chemical linkage capable of enzymatic or chemical cleavage. One of ordinary skill would therefore be motivated to incorporate the dioxetane compound as an additional type of cleavable linker with a reasonable expectation of success.

11. Claims 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Summerton in view of Singh et al. (US Patent 6,514,700; February 2003). Summerton teaches methods for rapidly detecting and isolating target nucleic acid sequences from a polynucleotide containing solution (Abstract, lines 1-3).

Regarding claim 16, Singh teaches a method wherein the hydrolytic cleavage is performed with a solution that also contains hydrogen peroxide (col. 9, lines 26-37, where hydrogen peroxide is used in oxidative cleavage of the linker).

Regarding claim 17, Singh teaches a method wherein the hydrolytic cleavage is performed with a solution that contains a mineral acid (col. 9, lines 10-15, where HCl is included in a cleavage reaction).

It would have been prima facie obvious to one of ordinary skill in the art to substitute hydrogen peroxide and mineral acid for the base or enzymatic cleavage taught by Summerton. It is standard in the art to adjust reaction conditions to achieve the most efficient combination of solvents or reagents appropriate to the specific experiment being conducted. As taught by Singh, there are multiple options for cleavage of a linkage, including, but not limited to "silyl groups being cleaved with fluoride, oxidation, acid bromine or chlorine; o-nitrobenzyl with light; catchecols with cerium salts; sulfides with singlet oxygen or enzyme catalyzed cleavage with hydrogen peroxide" (col. 9, lines 26-37). One of ordinary skill in the art would recognize the role that routine optimization and substitution of reagents play in the art, who would therefore be motivated to substitute hydrogen peroxide for the other types of linkages and cleavage options previously taught by Summerton, with a reasonable expectation of success.

12. Claims 36-37 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Summerton in view of Mukhamedgaliev et al. (1994, Uzbekskii Khimicheskii Zhurnal (6), p. 41-3) and further in view of Reinecke et al. (Macromol. Rapid Commun., 1996, vol. 17, no. 15-23) and further in view of Platz et al. (US Patent 5,418,130; May 1995) or Hatekeyama et al.

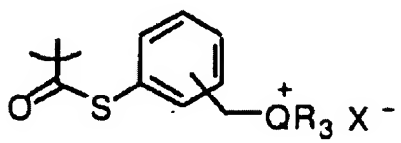
(JP2002060671; February 2002). Summerton teaches methods for rapidly detecting and isolating target nucleic acid sequences from a polynucleotide containing solution (Abstract, lines 1-3).

Summerton does not explicitly teach the inclusion of a quaternary phosphonium group as part of the nucleic acid binding portion of their invention, nor does Summerton teach linkage of the phosphonium group to a resin via a thioester linkage as displayed below. Mukhamedgaliev teaches the formation of quaternary phosphonium groups following reaction between methacrylol chloride and triphenylphosphine (see Abstract), which anticipates key components of the formation of the thioester recited in claims 36 and 37 as recited in Example 14 (p. 17 of the specification).

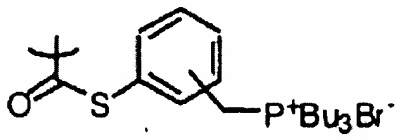
Mukhamedgaliev however, does not explicitly teach the structure of the compound synthesized or the attachment to the polymer using a thioester linkage.

Reinecke teaches a step that would anticipate the step of reacting the resin with 2-mercaptobenyl alcohol as exemplified in Example 14, that is missing from Mukhamedgaliev (Abstract, .

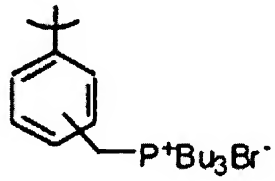
With regard to claim 36, Reinecke in view of Mukhamedgaliev teaches an embodiment which renders obvious a solid phase which comprises a thioester having the formula recited below.



With regard to claim 37, Reinecke in view of Mukhamedgaliev teaches an embodiment which renders obvious a solid phase which comprises a thioester having the formula recited below.



With regard to claim 41, Reinecke in view of Mukhamedgaliev teaches an embodiment which renders obvious a solid phase which comprises a thioester having the formula recited below.



It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to take the various teachings in the art at the time the invention was made, to modify a standard resin to attach a phosphonium group via a thioester linkage. As taught by Reinecke, the use of 2-mercaptobenzyl alcohol, or other aromatic thiols are useful in multi-step reactions, such as the PVC crosslinking analysis taught by Reinecke, because "aromatic thiols can easily substitute chlorine atoms in PVC under Sn2 mechanism, either in solution or melt conditions" and goes on to note further benefits of this type of reaction, including that there are no side reactions due to the high nucleophilicity and low basicity of sulfur (p. 15, paragraph 3).

The benefit of a resin with a phosphonium group attached has been established by previously noted references, including the teaching by Platz that the inclusion of an ammonium or phosphonium group within the sensitizer of their claimed invention "can impart water solubility to the sensitizer molecule" and also that "the substitution of halogen atoms, particularly bromine atoms, or psoralen molecules increases the binding constant of the sensitizer to DNA" (col. 4, lines 31-35 and col. 6, lines 28-32).. Therefore, one of ordinary skill in the art at the time the invention was made would be motivated to incorporate the separate teachings of Summerton, Mukhamedgaliev and Reinecke to arrive at a resin with a phosphonium group attached via a thioester linkage with a reasonable expectation of success.

13. Claims 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Summerton in view of Chopdekar et al. (US Patent 3,855,310; December 1974) and further in view of Hagashita et al. (US Patent 4,904,819; February 1999). Summerton teaches the isolation of nucleic acid molecules using cleavable linkage attachments between the nucleic acid binding portion and the surface of the solid support. Summerton teaches the limitations of claims 1, 6-10, 12, 19-22, 30, 32-35, 42-46, 48 and 50 as recited in the 102 rejection stated above. However, Summerton does not teach a linkage to the solid phase which is an alkylene group bonded to a trivalent phosphonium group, such as trialkylphosnium or triarylphosphonium.

With regard to claim 38, Stern teaches an embodiment wherein the cleavable linker portion of the solid phase is an alkylene group of at least one carbon atom bonded to a trialkylphosphonium or triarylphosphonium, nucleic acid binding position and is cleavable by means of a Wittig reaction with a ketone or aldehyde (col. 1, lines 9-17). Stern does not teach

the intricate details of the Wittig reaction as recited in claims 39 and 40. Hagashita teaches the use of a Wittig reaction in the synthesis of bicyclic sulfonamide derivatives (Abstract).

With regard to claim 39, Hagashita teaches an embodiment of claim 38, wherein the Wittig reaction forms a ylide by deprotonation with an alkoxide salt or hydride salt base in an aprotic organic solvent and the ylide reacts with a carbonyl compound selected from aliphatic and aromatic aldehydes and aliphatic and aromatic ketones (col. 6, lines 29-62, where the base treatment includes sodium hydride).

With regard to claim 40, Hagashita teaches an embodiment of claim 39, wherein the solvent is selected from THF, diethyl ether, p-dioxane, DMF and DMSO and the carbonyl compound for reaction with the ylide is acetone (col. 6, line 29 to col. 7, line 15, where tetrahydrofuran or dimethylformamide were noted as a potential solvents and acetone were noted).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the teachings in the art of the inclusion of triphenylphosphine containing compounds attached to a resin, as exemplified by Stern and Hagashita and to incorporate this type of linkage into the nucleic acid isolation technique taught by Summerton. As taught by Chopdekar, triphenyl phosphine groups "find use in a wide variety of processes; the ability of this typical compound to be selectively oxidized to triphenyl phosphine oxide permits its use in processes wherein a particular group must be selectively reduced" (col. 1, lines 9-17). The versatility of the triphenyl phosphine compound in reductive reactions would be obvious to one of ordinary skill in the art who would therefore be motivated to include the triphenyl

phosphine group into the solid phase binding of nucleic acids taught by Summerton with a reasonable expectation of success.

Conclusion

Claim 31 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie K. Mummert whose telephone number is 571-272-8503. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0872. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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CYNTHIA WILDER
PATENT EXAMINER
11/14/2005

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